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**Medical Staff Conference**

# Postmenopausal Osteoporosis

## Toward Resolution of the Dilemma

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.*

DR. SMITH:* *Of all of the disorders resulting in too litle bone, postmenopausal osteoporosis is the most prevalent. It is a very important cause of pain and disability. In the elderly it may also be indirectly a cause of death through increasing the risk of hip fractures.*

*Dr. Gilbert Gordan has devoted many years to the study of osteoporosis. We are fortunate to have him here today to summarize current knowledge about that frequent and debilitating disorder.*

DR. GORDAN:† Although sexually-determined bone loss is evident from paleopathologic studies of ancient bones (Armelagos,[1] Perzigian[2,3]), the relation of osteoporosis to the menopause was not clearly described until Fuller Albright made the connection in 1940.[4] The only previous suggestion of such a relationship was made by Bruns in 1882,[5] who noted that before the age of 50 hip fractures occur six times more frequently in males than in females. After the age of 50, the situation changes dramatically and for every fracture in men there are many more fractures in women. Albright also based his concept on clinical observation.

Albright made three observations leading to the concept of postmenopausal osteoporosis.[6,7] *First,* he noted that of his patients with osteoporosis almost all were women and all of these were postmenopausal. *Second,* results of balance studies carried out in these patients showed negative clacium and phosphate balances and elevated serum phosphate levels. *Third,* and very important, 1 mg of stilbestrol a day caused a reversal of all of these biochemical abnormalities. Albright also found that methyltestosterone similarly reversed the negative calcium and phosphate balances and caused nitrogen retention. He postulated that during the reproductive years sex hormones store up calcium in maternal bones for the needs of the fetal skeleton, and that loss of sex hormones at the menopause leads to bone loss. In 1968 Yendt and Gagne found that the serum calcium levels of women average 0.2 to 0.3 mg per 100 ml lower than those of men.[8] Mario Werner (then at the University of California, San Francisco) showed that serum calcium levels fall at the menarche and rise again at the menopause.[9] And Greenberg and associates showed in 1960 that serum phosphate levels rise in women after the age of 50, but do not rise in men.[10] Since estrogens inhibit bone resorption and lower serum calcium and phosphate levels, it is quite likely that during the reproductive years, estrogens restrain osteolysis, lower serum calcium and phosphate levels, and build up skeletal reservoirs of calcium.

Albright proposed an additional hypothesis re-

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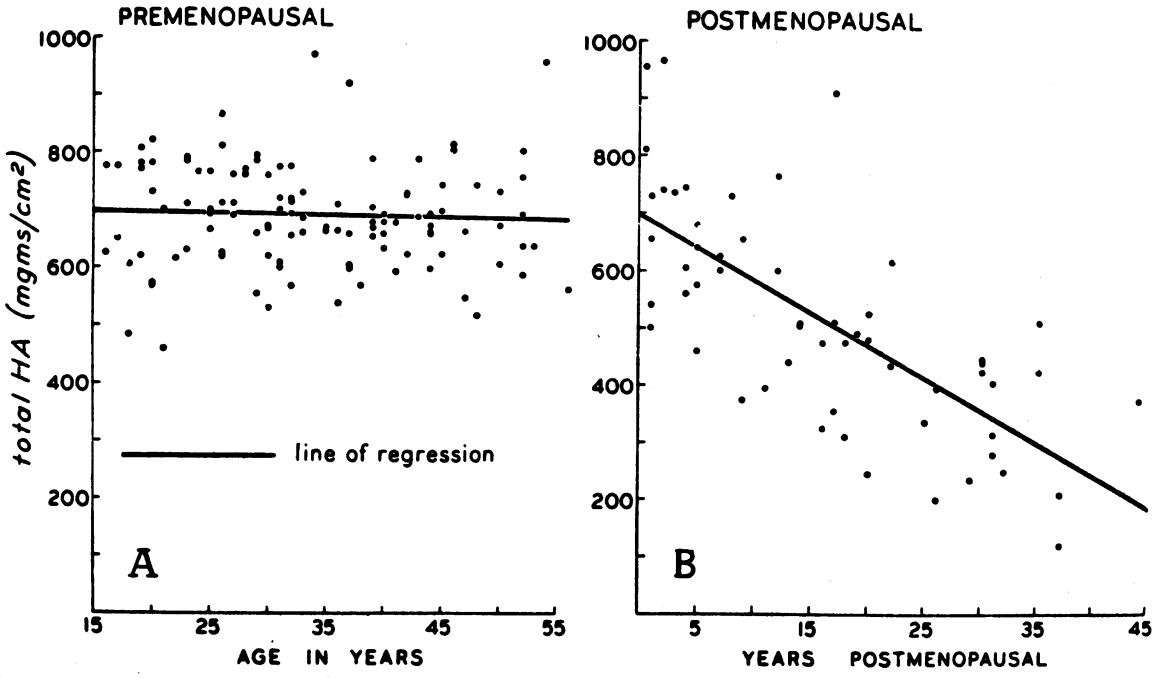


**Figure 1.**—Bone mineral mass of women before and after the menopause. Note maintenance of normal premenopausal bone mass in women still menstruating in their 50's. Values for young women who have been castrated are graphed according to number of years postoöphorectomy. (Reproduced with permission of Meema S and Amer J Obstet Gynecol)

garding the mechanism of action of estrogen on bone. Noting that histologic sections of bone in postmenopausal osteoporosis do not show excessive bone destruction such as one sees in osteitis fibrosa, he postulated that estrogen acts by stimulating bone formation. This thesis was supported by studies in mice and pigeons in which estrogen does indeed stimulate bone formation. This occurs to such a degree that bone actually crowds out the marrow and causes anemia but this effect is restricted to these two species. I should note at once that, while Albright's concept of the relation of the menopause to bone loss is now well documented, it now appears that in our species estrogen affects bone *not* by stimulating anabolism but by inhibiting breakdown.[11]

At this point, I think it important that we define our terms. Osteoporosis, in Albright's words, means simply "too little bone." What bone exists, is *normally* calcified. Osteoporosis is not primarily a disorder of mineral metabolism but of *bone tissue.* Too little bone can come about as a result of a number of disorders, the most common being *immobilization,* or from an *excess of catabolic adrenal or thyroid hormones,* or from *hypogonadism,* or from *alcoholism.* Osteoporosis should not be confused with other bone diseases such as osteomalacia where there is a defect in bone mineralization or osteitis fibrosa where bone is rapidly broken down by the osteolytic action of excess parathyroid hormone. In my experience, the most common problems of differential diagnosis are not osteomalacia or osteitis fibrosa but other disorders causing back pain, wedged vertebrae and radiolucency, including metastatic carcinoma, myeloma, juvenile epiphysitis, spondylolisthesis, back strains, osteogenesis imperfecta and various radiological artifacts—or no discernible bone disease at all. Hypertrophic osteoarthritis is also a common cause of back pain but is clinically and radiologically quite distinct from osteoporosis. In fact, in a current paper Dequeker finds by quantitation of bone mass that the two conditions are mutually exclusive,[12] that is to say one cannot have two much bone and too little bone at the same time.

It is now crystal clear that the osteoporoses are a group of heterogeneous disorders all having in common poverty of bone tissue. Clinically, chemically, radiologically, kinetically and—especially—in their response to treatment, the osteoporosis of Cushing's syndrome or of immobilization is quite different from the common postmenopausal type. The osteoporoses all have in common thinning of the skin, in postmenopausal osteoporosis, Cushing's syndrome, thyrotoxicosis and osteo-

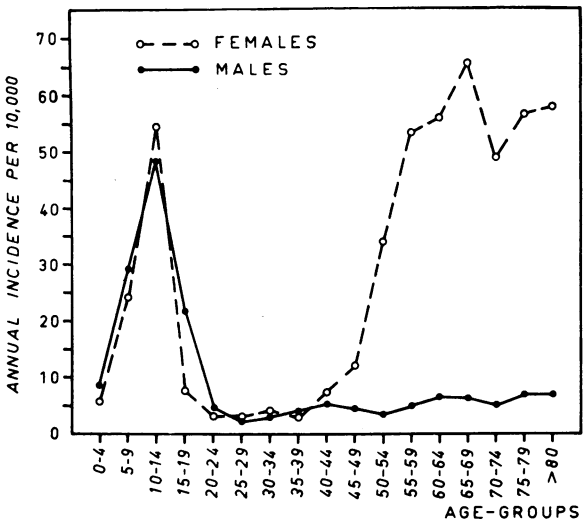


**Figure 2.**—Fractures of distal end of radius or ulna or both. Annual incidence in the city of Malmo. (Reproduced with permission of Alffram PA and J Bone Joint Surg[19])

genesis imperfecta. The fundamental defect in skin and bone is loss of collagen.

In the 36 years since Albright first described postmenopausal osteoporosis, considerable controversy has arisen. Some feel that osteoporosis is simply a "senile" disorder, not necessarily related to the menopause. Many have reported that osteoporosis does not respond to estrogens for no improvement is seen on x-ray studies of bone. Others have noted that while in most women with osteoporosis, back pain ceases in about three weeks, this effect is nonspecific. Still others have studied various osteoporoses by balance techniques and have noted no improvement, especially in "idiopathic osteoporosis." Recently, several prestigious investigators have actually called estrogen harmful because it reduces the rate of bone formation.

Before discussing each of these objections, I should like to register my own complaints. Many of these criticisms are based on studies of other types of osteoporosis, extrapolated to postmenopausal osteoporosis. In many cases it is not even certain that anything more than radiologic lucency was present—a subjective, nonspecific and often artefactual criterion. Much "osteoporosis" seems, unfortunately, to be in the eye of the beholder. The objections in the light of newer information have been neutralized.

We must first note confirmation by quantitative measures of sexual dimorphism in bone mass. At all ages and in all races, men have more bone than do women. There is also racial polymorphism: bone mass parallels skin pigmentation. Osteoporosis is rare in blacks and commonest in white females.[13] Women with brown or yellow skin occupy an intermediate position.[14] Two independent kinds of studies have conclusively related bone loss to loss of ovarian function. The Meemas in Toronto,[15] by elaborate and careful retrospective statistical studies, have shown that bone loss measured by cortical thickness or photon absorptiometry correlates with the menopause and not with age per se (Figure 1). This is conclusively shown in comparing young women who have been castrated with 50-year-old women who are still menstruating. In carefully controlled prospective studies of women following hysterectomy, using two methods for measuring bone mass, Aitken found that women whose ovaries are removed lose bone, while those whose ovaries are spared do not.[16] He has also shown by the double-blind technique that small doses of estrogen (mestranol, 20 $\mu$g per day) prevent this bone loss while placeboes do not.[17] In the crossover phase of this study, he even found some restoration of lost bone in women started on estrogen within three years after oöphorectomy, but none in women whose treatment was delayed for six years. Dalén and co-workers, using a different method, have also shown that women after oöphorectomy lose trabecular bone and that the bone loss occurs specifically in the three areas where postmenopausal women preferentially sustain fractures; the vertebrae, wrists and hips.[18] It has been known for many years that wrist fractures increase greatly in women but not in men after age 55 (Figure 2)[19] and the same selective increase has already been pointed out for hip fractures.[5,20] Hip fractures are of particular public health importance, accounting for considerable morbidity, hospital admissions and even mortality (Iskrant).[21]

From the data presented so far, I think it fair to say that osteoporosis occurs much more frequently in women than in men, and that the onset of osteoporosis is related temporally and causally to loss of ovarian function, either spontaneous at the menopause or surgical after oöphorectomy.

In the type of postmenopausal osteoporosis we could diagnose in the past, that is, "pathologic" osteoporosis with vertebral deformity and symptoms, as opposed to "physiologic" bone loss without clinical manifestations, we could not show restoration of bone on conventional x-ray films

following any kind of therapy. This failure to document bone increase results from the "bluntness" of our previous instruments for measuring bone mass and to the irreversability of far-advanced osteoporosis. The recent work of the Meemas and of Aitken shows that bone loss can be prevented by administration of estrogen and that bone can actually be restored if treatment is started early enough.

As to the placebo effect of estrogen on back pain, I must personally plead guilty to establishing this mechanism. In a double-blind study, evaluated by two psychiatrists, we found that estrogen relieved pain and induced well-being in 11 of 12 women with osteoporosis; but so did the psychoactive placebo dextroamphetamine-amobarbital (Dexamyl®). Even an inactive placebo (lactose) gave similar effects in about half the patients.[22] Urinary excretions of calcium and of a test load of strontium were not altered by the two placeboes but were both reduced by estrogen. In another group of patients treated with fluoxymesterone, there also was retention of calcium and strontium but there was no relief of back pain. The test period was only six weeks. It is uncertain whether placeboes would give sustained relief of pain and improved well-being as long as estrogens do. It is also possible that the androgen might have produced better results if administration was continued longer. In any event, I am pleased that women feel better during estrogen therapy but I do not take relief of pain per se as evidence that estrogens affect osteoporosis.

Perhaps the most cogent current question is whether estrogens produce a harmful lowering of the rate of bone formation. In 1963, Dr. Eisenberg and I showed that estrogens, androgens and anabolic agents (all really weak androgens), while inducing positive calcium balance, actually lower the bone accretion rate (as measured by bone-seeking tracers).[23] These findings have been widely confirmed and lead to the conclusion that these agents act, not by stimulating bone formation, but by inhibiting bone breakdown. I suppose accretion falls because of the internal homeostasis of bone where accretion and resorption are necessarily normally coupled. As a corollary, in advanced osteoporosis, one should not expect to see much new bone formation but only a cessation of the destructive process. This, of course, is locking the stable door after the horse is gone. I was very pleased in 1969 when Jenifer Jowsey's microradiography confirmed our findings by showing a reduction of bone resorption surface in biopsy specimens from women receiving conjugated estrogens (Premarin®), 2.5 mg a day.[24] But in 1972, she and Riggs reported that the amount of bone formation surface dropped to one eighth of the bone resorption surface on long-term estrogen treatment.[25] This brings up some interesting points on "quantitative" microradiography. This technique requires a bone biopsy specimen and quantitation of those surfaces where formation and resorption appear to be taking place. At best this gives an area, *but an area is not a rate.* Conflicting results have been reported. In Minnesota, postmenopausal osteoporosis is associated with normal formation and excessive resorption; in Paris, resorption is normal and formation decreased.[26] There may be technical reasons for these differences, but I think it clear that microradiography is a very tricky technique. Does estrogen harm bone? I think the clinical information to the contrary is more illuminating and less controversial.

Between 1948 and 1955 I started a prospective study on 220 women with postmenopausal osteoporosis to compare estrogens with androgens and anabolic agents.[27] Most of the anabolic agents were chemical derivatives of testosterone whose anabolic activity had been identified by growth of the levator ani muscle. Since the genital effects of estrogens and androgens are undoubted drawbacks, I hoped that anabolic agents with less genital activity would be the answer to a maiden's prayer. Unfortunately, in a long-term treatment the androgenic activity of such anabolic agents was poorly tolerated by postmenopausal women. They also appeared to be far less effective in preventing fractures than were the estrogens. As a result, there was a change to estrogen therapy in almost all women in this study.

Now, 28 years later, we still have 24 of the original 220 women taking estrogens. They came to us originally for very advanced osteoporosis with vertebral fractures and considerable loss of bone. Today they are up and around in their usual activities and fractures are no longer occurring. If estrogens had reduced the bone formation rate to one eighth that of resorption, these women should have no bone at all. Therefore, I am unable to agree that estrogens exert a detrimental effect on bone. In support of our observations it has recently been shown by the use of radiocalcium kinetics that in untreated postmenopausal women there are statistically significant

deviations from the premenopausal norm in that bone resorption exceeds bone formation.[28] In 25 women given estrogens the kinetic aberrations which lead to bone loss and postmenopausal osteoporosis did not occur. I think it is therefore clear that the postmenopausal changes leading to bone loss are preventable and that "senile" osteoporosis of women, like "senile" vaginitis, is not the inevitable consequence of aging but the result of hormone deficiency. This is totally preventable by small dose estrogen prophylaxis.

Recently considerable attention has been given to the possibility of increased risk among estrogen treated patients for the development of uterine cancer.[29,30] This disorder is heralded by vaginal bleeding and is treatable if caught at an early phase. We have handled this as follows: Whenever breakthrough bleeding occurred, except at the time of withdrawal of estrogen, the patient was referred to her gynecologist, and usually a dilation and curettage (D and C) was carried out. Today either aspiration biopsy study or other simple office procedures (such as jet-wash) without general anesthesia may be utilized effectively for diagnostic purposes to rule out early endometrial neoplasia. In 4 percent of our patients there were endometria that were so sensitive to estrogenic stimulation that the problem of repeated breakthrough bleeding was particularly troublesome and could not be controlled by converting the endometrium with a progestational steroid.

After several D and C's showing only benign endometrial hyperplasia, it is tempting to assume that subsequent episodes of bleeding at times other than following withdrawal of estrogen are also of benign origin. Our experience leads us to the opposite conclusion. All such episodes must be thoroughly investigated since we have encountered three cases of endometrial carcinoma in our 220 estrogen-treated women. These occurred at the 8th to 16th years of estrogen therapy. The peak incidence of endometrial cancer, at ages 60 to 64, has remained constant in this country at 80 per 100,000 women per year as measured in the Second and Third National Cancer Surveys (1947-1948 and 1969-1971). At that rate, we should have seen one or two cases. Actually we saw three, not significantly different in this small series of 220 osteoporotic women. Of course, every case of endometrial cancer is of concern despite the low mortality in this disease and the fact that it is a rare cause of death in this country (2,252 deaths in 1974). Since the endometrium is an estrogen-sensitive tissue, a possible relation between estrogens and endometrial cancer has often been suspected (Gusberg, 1975).[31] In 1975, Smith and co-workers and Ziel and Finkle reported an increased use of exogenous estrogens in women with endometrial cancer. These data undoubtedly reflect increased detection, probably because estrogens cause uterine bleeding which in turn leads to microscopic examination of the endometrium and therefore to early detection of endometrial carcinoma. In a study where this factor was controlled, Dun and Bradbury[32] and Pachecc and Kempers[33] found estrogen usage equal in women with endometrial carcinoma and women simultaneously admitted for postmenopausal bleeding from benign endometrial causes. There is no evidence of increased mortality from endometrial carcinoma. In fact, Cramer, Cutler and Christine[34] (1975) of the National Cancer Institute report that mortality is actually decreasing. Nonetheless, every case of bleeding-not-according-to-plan requires complete gynecologic investigation with histologic examination of the endometrium. Estrogen-induced endometrial hyperplasia and bleeding will predictably increase the detection of early endometrial carcinoma and should thereby reduce mortality, just as the Papanicolaou smear did for cervical cancer.

This year, Fuller Albright would have been 76 years old. He was a uniquely original thinker, a superb clinician, an intuitive investigator, a delightful person and a good friend. It gives me particular pleasure to conclude today's presentation by summarizing recent evidence supporting his basic concept of the central role of estrogens in postmenopausal osteoporosis.

*First:* loss of ovarian function is rapidly followed by loss of bone.

*Second:* small prophylactic doses of estrogen prevent this bone loss.

*Third:* menopausal women who have already lost enough bone to cause deformity, fractures, loss of height and invalidism, cease having fracture and losing height when given estrogen replacement therapy.

**REFERENCES**

1. Armelagos GJ: Disease in ancient Nubia—Changes in disease patterns from 350 B.C. to A.D. 1400 demonstrate the interaction of biology and culture. Science 163:255-259, 1969

2. Perzigian AJ: Osteoporotic bone loss in two prehistoric Indian populations. Am J Phys Anthropol 39:87-96, 1973

3. Perzigian AJ: The antiquity of age-associated bone demineralization in man. J Am Geriatr Soc 21:100-105, 1973

4. Albright F, Bloomberg E, Smith PH: Postmenopausal osteoporosis. Trans Assoc Am Physicians 55:298-305, 1940

5. Bruns P: Die allgemeine Lehre von den Knochenbruchen. Deutsche Chirurgie 27:1-400, 1882

6. Albright F, Smith PH, Richardson AM: Postmenopausal osteoporosis: Its clinical features. JAMA 116:2465-2474, May 31, 1941

7. Albright F: Osteoporosis. Ann Intern Med 27:861-882, 1947

8. Yendt ER, Gagne RJA: Detection of primary hyperparathyroidism, with special reference to its occurrence in hypercalciuric females with "normal" or borderline serum calcium. Canad Med Assoc J 98:331-336, Feb 1968

9. Werner M, Tolls RE, Hultin JV, et al: Influence of sex and age on the normal range of eleven serum constituents. Z Klin Chem Klin Biochem 8:105-115, 1970

10. Greenberg BG, Winters RW, Graham JB: Normal range of serum inorganic phosphorus and its utility as a discriminant in the diagnosis of congenital hypophosphatemia. J Clin Endocrinol Metab 20:364-379, 1960

11. Eisenberg E: Effects of androgens, estrogens and corticoids on strontium kinetics in man. J Clin Endocrinol Metab 26:566-572, May 1966

12. Dequeker J, Burssens A, Creytens G, et al: Aging of bone: Its relation to osteoporosis and osteoarthrosis in postmenopausal women. Front Hormone Res 3:116-130, 1975

13. Trotter M, Broman G, Peterson RR: Densities of bone of white and Negro skeletons. J Bone Joint Surg 42A:50-59, 1960

14. Goldsmith NF, Johnston JO, Picetti G, et al: Bone mineral in the radius and vertebral osteoporosis in an insured population —A correlative study using $^{125}I$ photon absorption and miniature roentgenography. J Bone Joint Surg 55:1276-1293, Sep 1973

15. Meema S, Meema HE: Menopausal bone loss and estrogen replacement. Is J Med Sci, 1976 (in press)

16. Aitken JM, Hart DM, Anderson JB, et al: Osteoporosis after oöphorectomy for non-malignant disease in premenopausal women. Br Med J 2:325-328, 1973

17. Aitken JM, Hart DM, Lindsay R: Oestrogen replacement therapy for prevention of osteoporosis after oöphorectomy. Br Med J 3:515-518, 1973

18. Dalén N, Lamke B, Wallgren A: Bone-mineral losses in oöphorectomized women. J Bone Joint Surg 56A:1235-1238, Sep 1974

19. Alffram PA, Bauer GCH: Epidemiology of fractures of the forearm. J Bone Joint Surg 44-A:105-114, 1962

20. Alhava EM, Puittinen J: Fractures of the upper end of the femur as an index of senile osteoporosis in Finland. Ann Clin Res 5:398-403, 1973

21. Iskrant AP: The etiology of fractured hips in females. Am J Public Health 58:485-490, Mar 1968

22. Solomon GF, Dickerson WJ, Eisenberg E: Psychologic and osteometabolic responses to sex hormones in elderly osteoporotic women. Geriatrics 15:46-60, Jan 1960

23. Gordan GS, Eisenberg E: The effect of estrogens, androgens and corticoids on skeletal kinetics in man. Proc R Soc Med (London) 56:1027-1029, Nov 1963

24. Riggs BL, Jowsey J, Kelly PJ, et al: Effect of sex hormones on bone in primary osteoporosis. J Clin Invest 48:1065-1072, Jun 1969

25. Riggs BL, Jowsey J, Goldsmith RS, et al: Short- and long-term effects of estrogen and synthetic anabolic hormone in postmenopausal osteoporosis. J Clin Invest 51:1659-1663, Jul 1972

26. Bordier P, Tun-Chot S: Quantitative histology of metabolic bone disease. Clinics in Endocrinology and Metabolism 1:197-215, 1972

27. Gordan GS, Picchi J, Roof BS: Antifracture efficacy of long-term estrogens for osteoporosis. Trans Assoc Am Physicians 86:326-332, 1973

28. Heaney RP, Recker RR: Estrogen effects on bone remodelling at menopause. Clin Res 23:535, Oct 1975

29. Smith DC, Prentice R, Thompson DJ, et al: Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 293:1164-1167, Dec 1975

30. Ziel HK, Finkle WDF: Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 293: 1167-1170, Dec 4, 1975

31. Gusberg SB: A strategy for the control of endometrial cancer. Proc R Soc Med (London) 68:163-168, Mar 1975

32. Dun LJ, Bradbury JT: Endocrine factors in endometrial carcinoma. Am J Obstet Gynecol 97:465-471, 1967

33. Pachecc JC, Kempers RD: Etiology of postmenopausal bleeding. Obstet Gynec 32:40-46, 1968

34. Cramer DW, Cutler SJ, Christine B: Trends in the incidence of endometrial cancer in the United States. Gynecol Oncol 2: 130-143, 1974